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EXAMINER	
NIKODEM,D	
ART UNIT	**PAPER NUMBER**
1633	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No.	Applicant(s)	
	09/215,257	FIRE ET AL.	
	Examiner	Art Unit	
	David Nikodem	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *7,24 and 36-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-23,25-35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4-7,9,11* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Claims election

1. Applicant's election with traverse of Group I in Paper No. 10 is acknowledged.

The traversal is on the ground(s) that 1) the generic claims (i.e. claims 1-5, 10-18, 21, 22, 28-31, 34 and 39) should not be restricted to either animals or plants, 2) it would not be burdensome to search all the claims as one invention based on the difference between transient inhibition of gene expression (i.e. *in vitro*) and stable gene expression inhibition (i.e. transgenic animal), and 3) a proper search of the generic claims would include a search of both animals and plants. This is not found persuasive because of the following reasons:

2. Firstly, the argument that "generic claims must be searched and examined without regard to the source of the cells" is improper. The success of the method of using dsRNA to inhibit gene expression is subject to a variety of cellular factors that include the origin of the cell. Animal cells are vastly different from plant cells, each with unique phenotype that may necessitate different delivery methods and that may affect success of the claimed method. A successful method in animals is not predictive of success in plants, and *vice versa*. Separate searches are required for the claimed methods utilized in animals and for in plants. Election of the generic claims to animals results in the examination of all the generic claims with regard to animal cells.

3. Secondly, nothing in the generic claims states that expression of the dsRNA is stable. It is well known that RNA is unstable and degrades over time within a cell. The

claims are read in light of the specification and it appears that nothing in the specification teaches the construction of transgenic animals. In view of RNA unstability and lack of adequate teaching for transgenic animal generation, the generic claims are considered as transient expression of the dsRNA, whereas the claims drawn to transgenic animals are considered stable expression.

4. Thirdly, the search for methods of use in animals is separate and not coextensive with the search for methods of use in plants. Because these inventions are distinct and have acquired a separate status in the art as shown by their different classification and different scientific considerations (see paragraph 2 of the instant office action), restriction for examination purposes as indicated is considered proper.

5. Thus, the requirement for restriction is still deemed proper and is therefore made FINAL.

6. Claims 7, 24 and 36-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6, 8-23, 25-35 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. The use of the language "portion" in the claims to refer to a region of a target gene is indefinite with regard to what stretch of nucleotides define a "portion." The use of this broad claim language renders the claims indefinite as to the nucleic acid sequence of the target gene necessary to practice the invention as claimed.

9. In claim 12, the use of the hyphen in "loss-of" is vague as to why a hyphen is necessary. Appropriate correction or explanation is required.

10. In claim 35, the claim is dependent on itself. The claim can not be interpreted as written. Appropriate correction is required. However, for purposes of examination herein, the claim will be considered to be dependent on claim 22.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-6, 8-23, 25-35 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. The claims are drawn to a method to inhibit expression of a target gene in a cell comprising introduction of double stranded RNA (dsRNA) with an identical nucleotide

sequence to a portion of a target gene into the cell in an amount sufficient to inhibit expression of said target gene, and a method to inhibit expression of a target gene comprising providing an organism containing an expressed target gene in a target cell, contacting a dsRNA with the organism and introducing the RNA into the target cell, wherein one strand of RNA is able to duplex with a portion of the target gene. The claims are further drawn to limitations of the base claims wherein said target gene is a transgene, a cellular, endogenous, or viral gene, wherein the cell is from an animal, an invertebrate animal, or a nematode, wherein the nucleotide sequence of said dsRNA is at least 50 bases in length, wherein the inhibition of target gene expression demonstrates a loss of function phenotype, wherein target gene expression is inhibited by at least 10%, wherein one strand of the dsRNA is self-complementary or both strands are complementary, wherein the initiation of RNA duplex is inside or outside of the cell, wherein the RNA is introduced within the body cavity of an organism, wherein the RNA is introduced by extracellular injection, or by feeding a duplex forming RNA-containing organism, wherein the dsRNA is produced by an expression construct, and wherein said methods are used in a kit.

14. The claims read broadly on two methods and kits using <u>any</u> dsRNA to target <u>any</u> gene in <u>any</u> organism. The specification teaches an example where a single species of a large genus of using the method has been reduced to practice, i.e. the methods of target gene expression inhibition using dsRNA for the genes Mex3 and unc22A in *C. elegans*. The specification discloses success of the claimed methods in only one species and with only one allele for each of two genes. Therefore, although the

disclosed species within the genus has been adequately described, there is no description of success of said claimed methods using any other gene(s) in any other organism.

15. The success of the claimed methods varies from gene to gene and from organism to organism. The broadly drawn methods claim inhibiting gene expression with dsRNA of any gene in any organism. The general knowledge of the state of the art regarding dsRNA inhibition of gene expression is such that the structure of one or two target genes is not representative of the genus of all potential target genes. Varying structure of the DNA will cause varying degrees of accessibility of the dsRNA for the target gene from target gene to target gene. There is no description of how the structure of Mex3 and unc22A in *C. elegans*, relates to the structure of different alleles of other species and to different target genes. Thus, the common attributes or features of the genus are not described.

16. In view of aforementioned considerations, one of skill in the art would conclude that applicant was not in possession of said methods as claimed since a description of using said methods with only two genes in one organism is not representative of the genus as a whole and thus is insufficient to support the broadly drawn claims.

17. Claims 1-6, 8-23, 25-35 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method or kit to inhibit expression of a target gene in a cell comprising introduction of dsRNA with an identical

nucleotide sequence to a portion of a target gene into the cell in an amount sufficient to inhibit expression of said target gene, and a method to inhibit expression of a target gene comprising providing an organism containing an expressed target gene in a target cell, contacting a dsRNA with the organism and introducing the RNA into the target cell, wherein on strand of RNA is able to duplex with a portion of the target gene, wherein the target gene is Mex3 and/or unc22A and the organism is *C. elegans* , **does not reasonably provide enablement for** a method or kit to inhibit expression of any target gene in any cell comprising introduction of double stranded RNA (dsRNA) with an identical nucleotide sequence to a portion of a target gene into the cell in an amount sufficient to inhibit expression of said target gene, and/or a method to inhibit expression of a target gene comprising providing an organism containing an expressed target gene in a target cell, contacting a dsRNA with the organism wherein one strand of RNA is able to duplex with a portion of the target gene and introducing the RNA into the target cell wherein said target gene is a transgene, a cellular, endogenous, or viral gene, wherein the cell is from an animal, an invertebrate animal, or a nematode, wherein the nucleotide sequence of said dsRNA is at least 50 bases in length, wherein the inhibition of target gene expression demonstrates a loss of function phenotype, wherein target gene expression is inhibited by at least 10%, wherein one strand of the dsRNA is self-complementary or both strands are complementary, wherein the initiation of RNA duplex is inside or outside of the cell, wherein the RNA is introduced within the body cavity of an organism, wherein the RNA is introduced by extracellular injection, or by feeding a duplex forming RNA-containing organism, and wherein the dsRNA is

produced by an expression construct, for any organism and for any gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

18. The claims have been described in paragraph 13 of the instant office action. The specification teaches a method to inhibit expression of a target gene in a cell comprising introduction of dsRNA with an identical nucleotide sequence to a portion of a target gene into the cell in an amount sufficient to inhibit expression of said target gene, and a method to inhibit expression of a target gene comprising providing an organism containing an expressed target gene in a target cell, contacting a dsRNA with the organism wherein on strand of RNA is able to duplex with a portion of the target gene and introducing the RNA into the target cell, wherein the target gene is Mex3 and/or unc22A and the organism is *C. elegans* . The specification fails to teach said methods using any other gene in *C. elegans* or using any gene in any organism.

19. At first issue, the state of the art regarding the use of dsRNA to inhibit target gene expression is unpredictable. The specification fails to provide guidance to the skilled artisan on the parameters necessary for such method over the breadth of the broadly claimed invention. Numerous factors complicate the delivery of dsRNA to cells, which have not been shown to be overcome by routine experimentation. These include, the fate of the dsRNA (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of dsRNA function with regard to success of gene expression inhibition on different genes in different organisms, the fraction of dsRNA that binds to

the target polypeptide, the trafficking of the dsRNA within the host and/or within cellular organelles, the rate of degradation of the dsRNA, the *in vivo* stability of the dsRNA, the binding affinity (i.e. k_D) of the dsRNA for the target nucleic acid sequence, the minimum dsRNA concentration necessary to inhibit target gene expression, the mode of delivery to the organism, the formulation of the dsRNA for delivery, target accessibility, varying secondary and tertiary nucleic acid structure *in vivo*, interference of dsRNA binding to the target gene, and potential toxicity of the dsRNA to the host. These factors can differ dramatically based on the dsRNA, the delivery method, the delivery formulation, the target gene, and the organism being used. Furthermore,

20. At second issue, the state of the art at the time of filing and subsequently thereafter is such that the use of dsRNA to inhibit gene expression is unpredictable for any gene in any organism. The teachings of the instant application for success of this method for Mex3 and unc22A in *C. elegans* is not predictive of success for other genes in other organisms. The specification (page 31) discloses that "inhibition was not effective in all tissues." This supports the unpredictability of success for this method since not all tissues could be used for inhibition of gene expression. Furthermore, Wagner, *et al.* speculates (page 745) as to whether or not "a similar phenomenon exist in other organism" and that "whatever the mechanism might be, dsRNA mediated inhibition of gene expression will provide a useful alternative for working out gene function in *C. elegans* and, maybe, in other animals and plants."

21. Further support for unpredictability for of the claimed method is taught by Clemens, *et al.*. On page 1, the authors state that "some variability of efficacy has been

noted for different dsRNA probes that target the same gene." This evidence suggests that for each gene, a target sequence of specified length must be identified for successful target gene inhibition by dsRNA. Furthermore, it is well known that genes of homologous function can vary significantly from organisms to organism. Sharp teaches (page 141) that it is unknown that the method of gene expression inhibition by dsRNA would function in mammals and further that "perhaps some aspect of [dsRNA gene inhibition] occurs or can be induced in mammalian cells." Therefore, due to the unpredictable nature of this method, each dsRNA would have to be identified for more than just two target genes in more than just two tissues of more than just one species of organism to enable the methods over the broadly drawn scope as claimed.

22. Further support for unpredictability for of the claimed method is taught by Fire, *et al.* (Nature, 1998, 391:806-11). On page 810 the reference states that "double stranded RNA could conceivably mediate interference more generally in other nematodes, in other invertebrates and, potentially, in vertebrates." Applicants own suggestion of possible functionality of the claimed method with other genes in *C. elegans* and in other species of organisms directly supports the unpredictability of the claimed methods.

23. Thus, the identification of gene expression inhibition by dsRNA of two genes in one organism, and the lack of teachings of said method in for any other gene in any other organism, does not enable one skilled in the art to practice the invention over the scope as claimed. It would require undue experimentation for one skilled in the art to practice the invention as claimed. The amount of experimentation would require the *de novo* trial and error identification of every specific dsRNA nucleotide sequence that is

hypothesized to inhibit gene expression of a specific target gene in a specific organism. The amount of experimentation would further require identifying an dsRNA(s) that is in a readily administerable form, with an acceptable level of toxicity and that will be properly processed *in vivo* so that a treatment effect is seen. Therefore, the claimed method is unpredictable over the known art for any gene in any organism. In view of such the invention is not enabled over the scope as claimed.

24. Prior art does not teach or fairly suggest dsRNA gene expression inhibition.

25. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Nikodem whose telephone number is (703) 308-8361. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3230 for regular communications and (703) 305-3230 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or Proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

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June 1, 2000

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